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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	6

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/203,676	Zalutsky
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-47* is/are pending in the applica

4a) Of the above, claim(s) *22-43* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-21 and 44-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

18) ☐ Interview Summary (PTO-413) Paper No(s) _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 1-47 are pending. Claims 22-43 remain withdrawn from consideration. Claims 1-21 and 44-47 are under consideration.

3. The rejection of claims 1-4, 8, 11-21 and 44 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed, is withdrawn.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 21, 44, 45 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnett et al. (CA 2094658). Claims 1-2 are drawn to a composition for internally labeling a cell comprising a ligand linked to an oligopeptide, said oligopeptide being linked to a label, wherein the oligopeptide comprises at least one positively charged amino acid, and at least one D-amino acid, but does not comprise two or more contiguous L-amino acids, wherein the L-amino acids are separated from one another by one or more positively charged D-amino acids. Claim 21 embodies a fluorescent label. Claim 44 specifies that the oligopeptide comprises at least two positively charged amino acids. Claim 45 embodies the ligand comprising a fragment of an antibody. Claim 46 specifies that said fragment comprises an immunoglobulin light chain variable and heavy chain variable region. Claim 47 embodies the ligand comprising a single

chain antibody. Barnett et al disclose a chemical conjugate for the intracellular delivery of biochemical agents comprising a biological agent chemically coupled to a carrier peptide, the carrier peptide preferentially comprising mostly positively charged amino acids, at least 50% of which are in the D-isomer form. Barnett et al disclose the preferred embodiments of the carrier peptide as consisting of 8 to 10, preferably 9 D-arginine residues. Barnett et al disclose the chemical conjugate as useful for the delivery of diagnostic agents. As the preferred embodiment peptide does not exceed 10 amino acid residues, the preferred embodiment peptide cannot contain two contiguous L-amino acids.

6. Claims 1-5, 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett et al. (CA 209465) in view of Reist et al (Cancer Research, 1996, Vol. 56, pp. 4970-4977) and Zalutsky et al (US 5,302,700). Claims 1-2 are drawn to a composition for internally labeling a cell , comprising a ligand linked to an oligopeptide, linked to a label, wherein the oligopeptide comprises at least one positively charged amino acid, and at least one D-amino acid, but does not comprise two or more contiguous L-amino acids, wherein the L-amino acids are separated from one another by one or more positively charged D-amino acids. Claims 3-5 are drawn in part to a composition for internally labeling a cell comprising a ligand being covalently bound to I-131 labeled oligopeptide via a labeling moiety of 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate), comprising at least one D-Lys, and one positively charged amino acid. Claims 9 and 10 are drawn to a composition comprising a monoclonal antibody that specifically binds EGRFvIII. Claim 11 embodies the oligopeptide as comprising a tyrosine residue. Claims 12 and 13 embody the oligopeptide as comprising D- arginine in addition to a D-tyrosine residue, and at least three D-arginines in addition to a D-tyrosine, respectively. Claim 14 embodies the oligopeptide comprising a D-lysine residue. Claims 15 and 16 embody the oligopeptide as comprising D-arginine in addition to a D-lysine residue, and at least three D-arginines in addition to a D-lysine, respectively. Claims 17-20 are drawn to the various compositions comprising a radionuclide.

For the reasons stated in paragraph 5, supra, Barnett et al teach a composition for internally labeling a cell comprising multiple D-arginine residues.. Barnett et al do not teach a ligand being covalently bound to I-131 labeled oligopeptide via a labeling moiety of 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate), comprising at least one D-Lys, and one positively charged amino acid nor a composition comprising a monoclonal antibody that specifically binds EGRFvIII. Reist teaches a composition comprising iodine 131 or iodine 125 in a 5-iodo-3-pyridine carboxylate labeled (pg 4970, column 2, 4th lines from bottom) monoclonal antibody against the EGFRvIII (pg 4970, column 2, lines 7-8 from bottom). Reist also teaches the benefits of carrying a positively charged moiety for resisting lysosomal degradation and enhancing cellular retention of the radiolabel (pg 4970, column 1, lines 7-15). Reist does not specifically teach D-amino acids and positively charged amino acids for resisting lysosomal degradation. Zalutsky teach the radioiodination of peptides via tyrosine or lysine. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a ligand comprsing the the a monoclonal antibody that specifically binds EGRFvIII, attached to the carrier peptide as described by Barnett. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Reist on the specific binding and internalization of the radiolabeled anti-EGFRVIII antibody in glioma, lung, breast and ovarian carcinomas.

7. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett et al (CA 209465) and Reist (Cancer Research, 1996) and Zalutsky (US 5,302,700) as applied to claims 1-5, 8-20 above, and further in view of Emery (Antibody Engineering, 1995). Claims 6 and 7 are drawn to a composition comprising a humanized antibody and interspecies antibody respectively, said antibodies specifically bind EGRFvIII . Reist et al do not teach the use of the humanized or interspecies antibody that specifically binds EGFRvIII. Emery teaches that the use of humanized or murine variable regions grafted onto human framework regions increases the

half-life of the antibodies, imparts greater effector functions by means of the human framework constant regions and avoids human anti-mouse hypersensitivity reactions. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a ligand comprising a humanized or interspecies monoclonal antibody that specifically binds to EGFRvIII which is covalently attached to the oligopeptide as taught by Barnett et al.. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Emery on the advantages of using humanized antibodies in clinical studies and the methods for making said humanized antibodies.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
October 21, 2001